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Review

Fatal carbamazepine induced fulminant eosinophilic (hypersensitivity) myocarditis: Emphasis on anatomical and histological characteristics, mechanisms and genetics of drug hypersensitivity and differential diagnosis

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ABSTRACT

The most severe adverse reactions to carbamazepine have been observed in the haemopoietic system, the liver and the cardiovascular system. A frequently fatal, although exceptionally rare side effect of carbamazepine is necrotizing eosinophilic (hypersensitivity) myocarditis. We report a case of hypersensitivity myocarditis secondary to administration of carbamazepine. Acute hypersensitivity myocarditis was not suspected clinically, and the diagnosis was made post-mortem. Histology revealed diffuse infiltration of the myocardium by eosinophils and lymphocytes with myocyte damage. Clinically, death was due to cardiogenic shock. To best of our knowledge this is the second case of fatal carbamazepine induced myocarditis reported in English literature.

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1. Introduction

Myocarditis is an inflammatory disorder of the myocardium with necrosis of the myocytes and associated inflammatory infiltrate.[1] It may be acute, subacute, or chronic, and the myocardium can be involved either focally or diffusely.[2] The signs and symptoms of myocarditis are related either to the actual inflammation of the myocardium or the weakness of the heart muscle that is secondary to the inflammation, and usually include chest pain, congestive heart failure and arrhythmias.[3] Generally myocarditis can be caused by infectious and non-infectious agents. The infectious agents most likely to cause myocarditis are: viruses (adenovirus and enterovirus), bacteria, fungi and protozoa. Non-infectious agents include systemic diseases, toxins and different drugs including antibiotics, diuretics, anti-inflammatory drugs, anti-convulsants, anti-psychotics and chemotherapeutic drugs.[1,3,4]

Carbamazepine is an anticonvulsant and specific analgesic for trigeminal neuralgia. The drug is widely prescribed for other neuropsychiatric disorders such as epilepsy, painful neuropathy and bipolar disorder.[5] Many side effects have been reported with the administration of the drug, but the most severe have been observed in the cardiovascular and haemopoietic systems.[6]

The aim of this case report is to draw the attention of the medical professionals to the very rare, but potentially fatal side effects of carbamazepine administration.

2. Case report

We describe a 41 year old man, with a recent history of epilepsy treated by carbamazepine.

The deceased was an otherwise healthy man admitted to the hospital with a severe allergic reaction complicated by Stevens–Johnson syndrome a week after initial administration of carbamazepine. The full blood count showed a marked eosinophilia (6.48×10^9 cells/L). The medical history nonetheless revealed no previous allergies, exposure to animals, pork ingestion or travel to exotic destinations. After one week of being hospitalised, his condition improved and he was discharged home. Two days later however, he was brought back to the hospital with shortness of breath. Blood tests and X-rays were performed and raised a suspicion of chest infection. Antibiotic treatment was introduced immediately. Nevertheless, early next morning, he showed clinical signs of heart failure with ECG showing tachycardia and tachyarrhythmia followed by cardiogenic shock and arrest. All attempts at resuscitation were unsuccessful. The deceased had no history of heart disease and cultures taken from the blood and cerebro-spinal fluid for a wide variety of viral and bacterial microorganisms were all negative.

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The autopsy was performed 48 h after death. The deceased was a well nourished 177 cm white male, weighing 86 kg. External examination revealed numerous naevi, particularly located on his chest and abdomen. There were areas of scaling skin over his face, anterior neck, chest, hips and scrotum consistent with the resolving skin rash of Stevens–Johnson syndrome. Examination of the internal organs showed a flabby heart that weighed 560 g. The pericardium was unremarkable without effusion. The main heart vessels were normally sited and the aorta showed no atheroma or change of calibre, measuring 4 cm in diameter above the aortic valve. The pulmonary artery measured 3.5 cm above the pulmonary valve. The coronary system of the heart displayed normal anatomy. Surprisingly however, within the first 2 cm, the left anterior descending artery was narrowed by an atheromatous plaque, to 50% of its cross-sectional area. The endocardium was not fibrotic and no mural thrombi were present. Right and left ventricular wall thicknesses were 0.7 cm and 1.9 cm, respectively. The myocardium (the free cardiac walls, interventricular septum and the papillary muscles) showed transmural, diffuse, tannish discoloration (mottling) (Fig. 1). The valve cusps and leaflets were thin and pliable.

The 1250 g right lung and 890 g left lung were severely congested and oedematous. The upper bronchial tree showed a minimal amount of mucus. There was moderate hepatosplenomegaly, the liver weighed 2560 g and the spleen 500 g. On sectioning, both liver and spleen were congested with no focal lesions. The brain weighed 1450 g, externally and on sectioning was unremarkable. There was no evidence of local/generalized lymphadenopathy. The other visceral organs were unremarkable except for marked congestion. Post-mortem tissue samples from heart, lungs, spleen and cerebro-spinal fluid for culture were negative for aerobic and anaerobic organisms and viruses including influenzas A and B viruses, respiratory syncytial virus, parainfluenza group, picornaviridae, human metapneumovirus, Epstein Barr virus, adenovirus, herpes simplex virus and varicella-zoster virus.

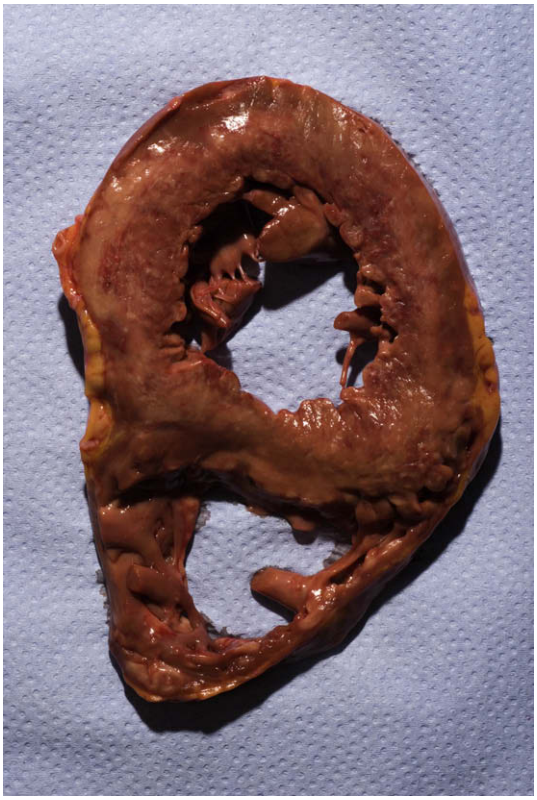

Fig. 1. Morphological appearance of the heart at autopsy revealing mottling of both left and right ventricle. The endocardium was unremarkable.

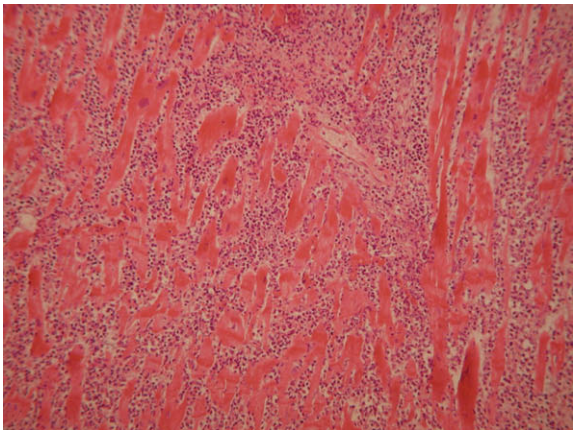

Fig. 2. Histological section of the heart showing mixed inflammatory cells infiltrate composed of eosinophils, mature T lymphocytes and occasional plasma cells. No giant cells are present.

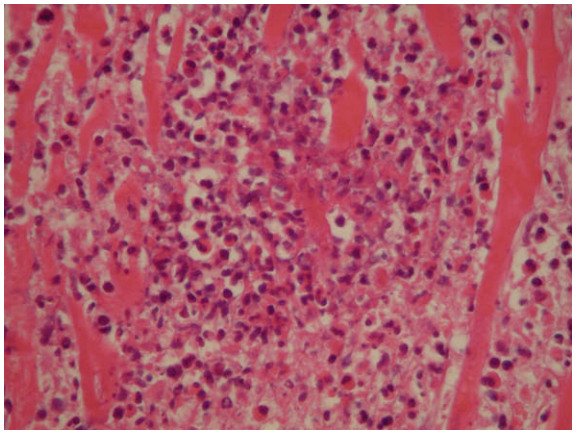

Fig. 3. A microabscess composed of eosinophils and polymorphonuclear leucocytes.

Microscopic examination revealed a diffuse mixed inflammatory cell infiltration of the myocardium of ventricles and atria. The infiltrate consisted predominantly of eosinophils without atypia, a smaller number of T lymphocytes and occasional plasma cells (Fig. 2). In places there were microabscesses composed of eosinophils and polymorphonuclear leucocytes (Fig. 3). There was widespread myocardial necrosis (Fig. 4), particularly in the left ventricle, and all lesions appeared to be of the same age. There was no fibrosis, granulomata, giant cells, microthrombi, viral inclusions, parasites or evidence of arteritis.

3. Discussion

Drug induced myocarditis was first recognized by French and Weller in 1942, who reported it in association with sulfonamide administration.[7] Macroscopically, hypersensitivity myocarditis (HM) is characterized by similar morphology of the myocardium of all four cardiac chambers.[8,9] Histologically, there is an interstitial inflammatory infiltrate which may be focal or diffuse typically consisting of eosinophils and mononuclear cells, particularly lymphocytes, as well as occasional plasma cells.[10] Myocyte necrosis is not a prominent feature of HM, except in fulminant cases.[11,12] Giant cells and ill-formed granulomas may be present, while granulation tissue and fibrosis are typically absent. Lesions appear to be synchronized.[9,10] The time from initial drug exposure to the

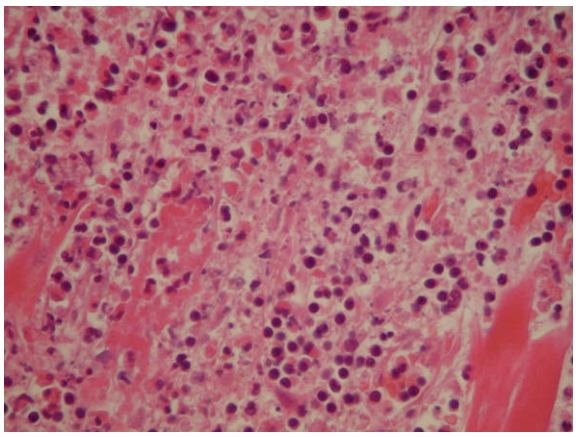

Fig. 4. A focus of myocardial necrosis.

development of hypersensitivity myocarditis may vary from hours to months. A variety of different drugs are known to be associated with HM including sulfonamides, izoniazid, penicillin, tetracyclines, phenylbutazone, thiazide diuretics, methyldopa, cocaine and streptomycin.[13] There have been reports of HM following tetanus vaccination[14] use of herbal medication Ma Huang[15] and clozapine.[16] It is difficult to establish an incidence of HM in the general population. The general autopsy reports record the incidence of 0.04–0.5%.[17] There is a growing literature of incidence rates of HM among heart transplant candidates. Reports of HM in explanted hearts have put this particular incidence rate between 2.4% and 7.2%.[18]

Hypersensitive drug reactions are currently explained by the hapten and pro-hapten models. Haptens, which are small chemically reactive compounds, bind to proteins or peptides and modify them. Haptens are then digested and presented on the surface of the cells to T cells as hapten-modified peptides.[19] Due to a delayed-type hypersensitivity response, eosinophil-stimulating cytokines such as interleukin-5[20] are released by the activation of T lymphocytes. In order to become chemically active haptens, pro-haptens need to undergo an intermediate metabolic step.[21] Recently, the p-i concept – 'direct pharmacological interaction of drugs with immune receptors' – has been put forth to elaborate on the pharmacologic interaction of drugs with immune receptors.[22] The p-i concept proposes that under the following conditions: (1) a drug–T-cell interaction leading to an immune response with the drug–T-cell combination fitting into a T-cell receptor and (2) the interaction of the T-cell receptor with a MHC molecule, will lead to an exclusive T-cell stimulation and to a hypersensitivity reaction.[22]

It is thought that genetic factors are of great importance in drug hypersensitivity. Recent research has shown the existence of a link between HLA-class 1 alleles and the HIV-1 reverse-transcriptase inhibitor abacavir. Approximately 5% of treated HIV positive patients had multiple organs affected by the drug; the majority of these patients carried the HLA-B57 allele. This association was mostly verified among Australian Caucasians.[23] Other associations have been shown such as the association between carbamazepine and Stevens–Johnson syndrome among Han Chinese carrying the HLA-B*1502 allele,[24] allopurinol for treatment of gout and hyperuricemia among Han Chinese carrying HLA-B*5801[25] and nevirapine (non-nucleoside reverse-transcriptase inhibitor for HIV treatment) among a predominantly Caucasian cohort carrying the HLA-DRB1*0101 allele.[26]

The differential diagnosis of HM includes hypereosinophilic myocarditis (HeoM), idiopathic giant cell myocarditis (GCM), toxic myocarditis (TM) and parasitic myocarditis (PM).

Hypereosinophilic syndrome (HES) encompasses a wide range of clinical manifestations sharing three features: (a) a peripheral eosinophil count of greater than 1.5×10^9/L for longer than 6 months; (b) evidence of organ involvement, thus excluding benign eosinophilia; and (c) an absence of other causes of eosinophilia, such as parasite infestation, allergy, malignancy, and collagen-vascular disease.[27] Eosinophils in HES infiltrate multiple organs where they inflict tissue damage through the release of granule proteins, including eosinophil peroxidase, major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein. They also release proinflammatory cytokines (i.e., interleukin 1 alpha, tumour necrosis factor-alpha, interleukin 6, interleukin 8, IL-3, IL-5, GM-CSF, macrophage inflammatory protein), which attract more eosinophils and other inflammatory cells to the area. Cardiac involvement (HeoM) is the most common cause of mortality in HES. In the heart, the infiltration by eosinophils results in endomyocardial fibrosis, with subsequent development of congestive heart failure and death. This infiltration is necessary for tissue damage to occur because patients with peripheral eosinophilia due to other causes (e.g., eosinophilic pneumonia) do not develop pathology similar to HES.[28] Histologically HM usually reveals myocardial inflammation with myocyte necrosis and IL-5 activated and CD69 positive eosinophils. HeoM on the other hand shows predominant endomyocardial damage, prominent necrosis and fibrosis and non allergic, CD69 negative eosinophils.[29]

GCM is a rare and often rapidly fatal form of myocarditis of unknown aetiology. The majority of patients present with congestive cardiac failure or conduction disturbances. Many autoimmune disorders have been cited to be associated with GCM, including ulcerative colitis, rheumatoid arthritis and pernicious anemia. These associations, and the reproducibility of experimental GCM in Lewis rats by autoimmunization with myosin,[30] suggest that it is an autoimmune disorder dependent on CD-4 positive T lymphocytes. Further support for an autoimmune aetiology is the reported response to immunosuppressive therapy. Histologically GCM shows myocardial necrosis, a chronic inflammatory infiltrate composed of lymphocytes, plasma cells, eosinophils and multinucleate giant cells.

TM may be caused by direct drug toxicity due to different medications including lithium, doxorubicin, cocaine, numerous catecholamines, acetaminophen etc.[13] Histological features are different from those seen in HM and comprise non synchronized lesions of myocardial necrosis, necrotizing vasculitis, fibrosis, absence of eosinophils and occasional microthrombi.

The most common parasites causing PM are trypanosoma cruzi and brucei, trichinella spiralis, and, in the immunocompromised host, toxoplasma gondii. The diagnosis is usually based on the clinical findings and the laboratory data.

In our paper we presented the case of a 41 years old man recently diagnosed with epilepsy, who had developed Stevens–Johnson syndrome following one week of carbamazepine therapy. The medical history nonetheless revealed no previous allergies, exposure to other drugs or animals, pork ingestion or travel to exotic destinations. To our knowledge there was no recent administration of prescribed or non prescribed drugs apart from carbamazepine. Antibiotic treatment was introduced a day before the deceased died. Cultures taken from the blood and cerebro-spinal fluid for a wide variety of viral and bacterial microorganisms were all negative. However, toxicology was not undertaken during the first or second admissions and the initial blood samples from the first admission had been disposed of by the time the post-mortem was undertaken. This could be regarded as a study limitation, but based on careful exclusion of all other possible causes we strongly believe carbamazepine was the culprit.

The heart was hypertrophic weighing 560 g (normal range 360–380 g) which was an enlargement of approximately 30% beyond

the upper 95% confidence limit of a reference population, with thickening of myocardium, particularly left ventricular wall and interventricular septum.

Cardiac hypertrophy may be secondary to physiological demand or pathological stress. Physiological hypertrophy occurs as an adaptive response to increased physical demand such as due to regular exercise (e.g. in athletes) or alteration in physiological constitution (pregnancy).[31]

These changes may reach striking proportions. Left ventricular wall thickness varies from 1.0 cm to 1.1 cm in normal individuals. In trained atheletes left ventricular wall thickness may reach 1.3 cm and may have 60% more mass in the left ventricular myocardium compared to average individuals.

Pathological hypertrophy is caused by compensatory changes in the ventricle to increased stress, such as increased pressure load (e.g. hypertension). In response to chronic overload the myocardium undergoes remodeling resulting in an increase in wall thickness and cardiac mass. Depending on the level and duration of stress, the cardiac mass may increase as much as twice that of the average weight (authors' observation).

Apart from the recently diagnosed epilepsy, the medical history of the deceased revealed no significant medical conditions. There were no records of his blood pressure.

However the family history revealed the deceased's 60 years old father as Hypertensive with a recorded and medically treated high blood pressure for over a decade.

In our case a significant proportion of the heart enlargement could be attributed to the widespread inflammatory infiltrate and oedema throughout the cardiac muscle of all chambers. However, it is doubtful whether this enlargement could have occurred within the 10-day time period prior to death.

There was no known medical history of cardiac disease such as Hypertension. However, it remains a possibility as previously undiagnosed pathology, especially in light of the patient's family history of hypertensive heart disease and microscopic findings of focal hypertrophic nuclear change in cardiac myocytes.

Such changes may precede documented hypertensive blood pressures in Adults. Wagners observation would support such a proposition. His studies involving electrocardiographic changes in individuals with hypertension in their teens, have shown increases in left ventricular mass, before arterial pressure reached levels considered abnormal in adults.[32] Furthermore some susceptible young individuals in their early twenties, with family history of high blood pressure may already have left ventricular hypertrophy consistent with hypertension without any clinical history of high blood pressure.[33]

The degree of myocyte necrosis in this case was particularly extensive. This has been documented in fulminant cases of HM.[11,12] In our case it could be postulated that because of the left ventricular hypertrophy present and the noncritical narrowing of the left anterior descending coronary artery, once left ventricular failure occurred during the second admission, associated hypoxaemia may have exacerbated the degree of myocyte necrosis.

4. Conclusions

There are various side effects reported with the administration of carbamazepine. Probably the most severe ones have been observed in the cardiovascular system[6] including HM. In a case of HM the heart is the target organ in a delayed-type of hypersensitivity response. Clinically, an allergic profile usually predominates (rash, fever) with an additional finding of cardiac manifestations. If new ECG changes occur in association with acute chest tightness and pain, mildly elevated cardiac enzyme levels and eosinophilia, one should suspect HM. If it is suspected, all drugs should be immediately withdrawn followed by corticosteroid therapy and myocardial biopsy which usually reveals prominence of eosinophils mixed with lymphocytes and some plasma cells and an absence of extensive necrosis or fibrosis. Anticonvulsive drug hypersensitivity can present with a wide spectrum of nonspecific symptoms, of which the prescribing clinician should be aware.

The previous reported case of HM in the literature was a teenage boy[34] and this case was a 41 year old man with no cardiac history. Both cases went for post-mortem as the cause of death was uncertain. It is possible that cases of HM are missed in the elderly who have a history of ischaemic heart disease and may be taking a multitude of different drugs. The death certificates are completed and no post-mortems are held.

5. Conflict of Interest

None declared.

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